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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/765,668	01/27/2004	David B. Rozema	Mirus.042.02	9890

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MIRUS CORPORATION
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EXAMINER

DUNSTON, JENNIFER ANN

ART UNIT	PAPER NUMBER
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1636

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07/26/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/765,668

Applicant(s)

ROZEMA ET AL.

Examiner

Jennifer Dunston

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 May 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 5,7,8,12,16 and 17 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 5,7,8,12,16 and 17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This action is in response to the amendment, filed 5/10/2007, in which claims 1-4, 6, 9-11, 13-15 and 18-20 were canceled, and claims 5 and 12 were amended. Currently, claims 5, 7, 8, 12, 16 and 17 are pending and under consideration.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Response to Arguments - Claim Objections

The objection of claims 5 and 12 has been withdrawn in view of Applicant's amendment to the claims in the reply filed 5/10/2007.

Response to Arguments - 35 USC § 112

The previous rejection of claims 5, 7, 8, 12-14, 16 and 17 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 5/10/2007.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an

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international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 5, 7 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Adams et al (US Patent Application Publication No. 2005/0153926 A1, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 2/12/2007 and has been rewritten to address the amendments to the claims.

Adams et al teach a method of delivery a polynucleotide to the cytoplasm of a cell, comprising (i) forming a composition comprising a water soluble polymer such as styrene-maleic anhydride, divinylether-maleic acid or poly(maleic anhydride-co-vinyl ether) and a nucleic acid linked to the polymer via an ethylene group (a functional group), where the polymer is further modified by the addition of esters, and (ii) administering the composition to a cell *in vitro* such that the cell endocytoses the polymer and nucleic acid (e.g. paragraphs [0037], [0057], [0081]-[0084], [0090]-[0093], [0162] and [0171]).

Response to Arguments - 35 USC § 102

The rejection of claims 12, 13, 16 and 17 under 35 U.S.C. 102(e) as being anticipated by Rozema et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 5/10/2007. Rozema et al do not teach the method step of forming a butyl vinyl ether-maleic anhydride alternating copolymer.

The rejection of claims 12, 13, 16 and 17 under 35 U.S.C. 102(e) as being anticipated by Trubetskoy et al, as evidenced by Rozema et al, has been withdrawn in view of Applicant's

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amendment to the claims in the reply filed 5/10/2007. Trubetskoy et al do not teach the method step of forming a butyl vinyl ether-maleic anhydride alternating copolymer.

The rejection of claims 12, 13 and 16 under 35 U.S.C. 102(b) as being anticipated by Tomlinson et al, as evidenced by Yu et al, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 5/10/2007.

The rejection of claims 12, 13, 16 and 17 under 35 U.S.C. 102(e) as being anticipated by Adams et al has been withdrawn in view of Applicant's amendment to the claims in the reply filed 5/10/2007. Adams et al do not teach the method step of forming a butyl vinyl ether-maleic anhydride alternating copolymer.

With respect to the rejection of claims 5, 7 and 8 under 35 U.S.C. 102(e) as being anticipated by Adams et al, Applicant's arguments filed 5/10/2007 have been fully considered but they are not persuasive.

The response asserts that Adams does not teach covalently linking hydrophobic groups to anhydride monomers in a styrene-maleic anhydride random copolymer. The response asserts that Adams only teaches that carboxylic acid groups can be used to attach nucleic acids (paragraph [0081] and [0090]-[0091]) or crosslinking agents (paragraph [0084]).

This is not found persuasive, because Adams et al teach that the hydrophobicity of the polymer is altered by attaching a monovalent moiety which is different in composition than the constituents of the bulk polymer and which does not bear a nucleic acid (e.g., paragraph [0057]). By, "monovalent moiety," Adams et al mean organic molecules with only one reactive functional group that attaches the molecule to the polymer backbone, such groups include long chain alcohols, amines, monomethyl esters, etc. (e.g., paragraph [0057]). Further, Adams et al

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teach that polymers that contain anhydride groups are capable of derivatization (e.g., paragraph [0081]). Adams et al specifically teach styrene-maleic anhydride as a polymer of the invention (e.g., paragraphs [0082] and [0083]). Thus, Adams et al teach covalently linking hydrophobic groups to anhydride monomers in a styrene-maleic anhydride random copolymer.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 5, 7, 8, 12, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tonge et al (US Patent No. 6,436,905, cited in a prior action; see the entire reference) in view of Maeda et al (US Patent No. 4,732,933, cited in a prior action; see the entire reference). This ground of rejection was made in the Office action mailed 9/18/2006 and has been extended to address claim 7 and 8, which were amended in the reply filed 12/5/2006.

Tonge et al teach a composition comprising a synthetic amphipathic polymer, including both hydrophobic groups and anionic hydrophilic groups and acting as a lipid-solubilizing agent (e.g. column 3, lines 49-52). Tonge et al teach that especially suitable polymers may be formed as alternating copolymers of maleic acid (or the anhydride thereof) with styrene, indene or a C₁₋₄ alkyl, e.g. methyl substituted styrene or indene, or with propyl (or isopropyl) or butyl vinyl ether

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(e.g. column 6, lines 27-31, 60-63). Tonge et al disclose examples of suitable polymers, including Poly(maleic anhydride-styrene) (a random copolymer), Poly(maleic anhydride-propyl vinyl ether), and Poly(maleic anhydride-butyl vinyl ether) (e.g. column 6, lines 60-63). Tonge et al teach the use of the polymers to administer drugs or DNA or RNA to cells to facilitate the uptake of the therapeutic agent into target cells (e.g. column 1, lines 31-45; column 12, line 40 to column 13, line 10).

Tonge et al do not teach covalently linking hydrophobic groups to anhydride monomers in the copolymer. Tonge et al do not teach the formation of hydrophobic esters of the butyl vinyl ether maleic anhydride copolymers or styrene maleic anhydride copolymers.

Maeda et al teach half-esterified styrene-maleic anhydride copolymers (SMA) for the delivery of the antitumor drug neocarzinostatin (NCS) to cells (e.g. column 4, lines 4-10; column 3, lines 25-47). Maeda et al teach the reaction of the maleic acid units to form hydrophobic esters of a monohydric alcohol or a monohydroxyalkyl ether of a di- or trihydric alcohol (e.g. column 1, lines 20-46). One embodiment disclosed by Maeda et al is neocarzinostatin-half butyl-esterified styrene-maleic acid copolymer complex (SMANX) (e.g. Example 1). Maeda et al teach the administration of the copolymer complex to tumor cells *in vivo* (e.g. paragraph bridging columns 6-7; column 3, lines 55-65). The compound is capable of entering the cell as evidenced by the effect of SMACS complex *in vivo* on the surviving percentage of mice with tumor cells implanted in the abdominal cavity (e.g. column 11, lines 58-68; column 12, lines 28-33; Table 6). Maeda et al teach that the addition of the half-esterified residues provides the advantage of providing lipid solubility while maintaining water solubility, which allows the

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composition to be administered as a water soluble composition (e.g. column 3, line 66 to column 4, line 10).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the maleic anhydride copolymers of Tonge et al to include the hydrophobic esters of Maeda et al because Tonge et al and Maeda et al teach it is within the ordinary skill in the art to use maleic anhydride-based copolymers for the delivery of macromolecules to cells.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to deliver the complex as a water soluble composition while maintaining the lipid solubility of the maleic anhydride-based copolymer as taught by Maeda et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 12, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al (US Patent Application Publication No. 2005/0153926 A1, cited in a prior action; see the entire reference) in view of Tonge et al (US Patent No. 6,436,905, cited in a prior action; see the entire reference). This rejection was made over claim 14 in the Office action mailed 2/12/2007 and has been rewritten to address the amendments to the claims in the reply filed 5/10/2007. In the reply filed 5/10/2007, claim 12 was amended to include a limitation of claim 14 (i.e., that the vinyl ether-maleic anhydride alternating copolymer of step (a) is a butyl vinyl ether maleic anhydride alternating copolymer).

The teachings of Adams et al are described above and applied as before.

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Adams et al do not specifically teach poly(maleic anhydride-co-vinyl ether) where the vinyl ether is butyl vinyl ether.

Tonge et al teach a composition comprising a synthetic amphipathic polymer, including both hydrophobic groups and anionic hydrophilic groups and acting as a lipid-solubilizing agent (e.g. column 3, lines 49-52). Tonge et al teach that especially suitable polymers may be formed as alternating copolymers of maleic acid (or the anhydride thereof) with styrene, indene or a C₁₋₄ alkyl, e.g. methyl substituted styrene or indene, or with propyl (or isopropyl) or butyl vinyl ether (e.g. column 6, lines 27-31, 60-63). Tonge et al disclose examples of suitable polymers, including Poly(maleic anhydride-styrene) (a random copolymer), Poly(maleic anhydride-propyl vinyl ether), and Poly(maleic anhydride-butyl vinyl ether) (e.g. column 6, lines 60-63). Tonge et al teach the use of the polymers to administer drugs or DNA or RNA to cells to facilitate the uptake of the therapeutic agent into target cells (e.g. column 1, lines 31-45; column 12, line 40 to column 13, line 10).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of delivering a nucleic acid to a cell using a poly(maleic anhydride-co-vinyl ether)-based composition to include butyl vinyl ether as the vinyl ether, which is taught by Tonge et al, because Adams et al and Tonge et al teach it is within the ordinary skill in the art to use poly(maleic anhydride-co-vinyl ether)-based compositions for the delivery of nucleic acid to a cell.

One would have been motivated to make such a modification in order to receive the expected benefit of defining the complete structure of the poly(maleic anhydride-co-vinyl ether) with a vinyl ether suitable for the delivery of nucleic acid as taught by Tonge et al. Based upon

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the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

The rejection of claims 13 and 14 under 35 U.S.C. 103(a) as being unpatentable over Tonge et al in view of Maeda et, is moot in view of Applicant's cancellation of the claims in the reply filed 5/10/2007.

With respect to the rejection of claims 5, 7, 8, 12, 16 and 17 under 35 U.S.C. 103(a) as being unpatentable over Tonge et al in view of Maeda et al, Applicant's arguments filed 5/10/2007 have been fully considered but they are not persuasive.

The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976). For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., *PPG*, 156 F.3d at 1355, 48 USPQ2d at 1355. In the instant case, Applicant has not provided evidence that the presence of the lipid of Tonge et al materially changes the characteristics of Applicant's invention. Tonge et al teach the use of the composition comprising the polymer and lipid for the delivery of a polynucleotide to the

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cytoplasm of the cell. Applicant has the burden of showing that the additional steps or components would materially change the Applicant's invention.

The response asserts that the Tonge et al clearly demonstrates that the primary component of their composition is a lipid-containing composition. The response asserts that the stated purpose of the polymer of Tonge et al is to solubilize the lipid in aqueous medium, and thus the polymer and lipid interact and have profound effects on one another. Further, the response asserts that the interaction would be expected to considerably alter the ability of the polymer to interact with cell membranes.

This is not found persuasive. The response does not provide objective evidence that the lipid in the composition of Tonge et al has a material effect on the delivery of the nucleic acid as compared to the claimed composition without a lipid. The basic and novel characteristics of the invention appear to be the delivery of a polynucleotide to the cytoplasm of a cell using a composition comprising a maleic anhydride-containing polymer. Tonge et al teaches the use of a maleic anhydride-containing compound to deliver a polynucleotide to a cell, and Maeda et al teach the use of esters of maleic anhydride-containing polymers to deliver a compound to a cell. Thus, the teachings of the reference are consistent with the intended outcome of the claimed method and do not appear to have an effect on the basic and novel characteristic(s) of the claimed invention.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

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Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

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applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

/JD/

CELIA E. GRIFFIN, Ph.D.
PRIMARY EXAMINER

